TOOLS OF RISK ANALYSIS

Applications of Epidemiology

I. Overview

II. Risk assessment epidemiology

A. Definition: a description of the change in the incidence rate of a disease due to a known change in the level of exposure to a cause

B. Purposes:
- guide public health policies
- guide the regulatory process
- assist in tort resolution

C. Foundations:
- basic science - nature of affect
- animal studies - describe potency

D. Growing importance of epidemiology: - usually the weakest & most difficult - but most important
- advances in methodology
- reduced reliance on animal research (species barrier)
- bases in law (opposition to the use of animals)

Extrapolation is objective
generalization - subjective
animals have a single exposure and the desire to produce an affect

III. Epidemiology - general

A. Definitions: the study of the distribution and determinants of disease in man

an observational science dealing with the environmental causes of diseases of human beings

B. Strengths
- human beings
- human lifestyles

C. Limitations
- non-experimental
- often qualitative

IV. Selected measures

A. Incidence rate

I = new cases/(population x time)

example: the incidence rate of leukemia is 10.1 cases per 100,000 person-years

B. Risk

R = new cases/population

example: the lifetime risk of developing leukemia is 700 per 100,000 persons, or 0.7%

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C. Relative incidence rate (relative risk, RR)
RR = the incidence rate in an exposed group divided by that in a non-exposed group
example: the RI of leukemia among rubber workers is 4.5 (base = 1.0)

D. Standardized mortality ratio effects of age, sex, race have been eliminated
SMR = the number of deaths observed (usually in an occupational group) divided by the number of deaths expected
example: among pliofilm workers the SMR is 337 (base = 100)

V. Study designs - general

A. Descriptive studies - the individual human being is not studied - a group is study - correlational studies
B. Follow-up (cohort) studies - analytic
a. prospective - into the future every individual is followed
b. retrospective - past most common

C. Case-control - less important for RA - selection of disease begin with people with and without disease & determine exposure
D. Proportional mortality ratio (PMR)

VI. Study designs - specific

A. The retrospective follow-up design

Example: 1165 rubber hydrochloride (pliofilm) workers followed-up from 1950-81 experienced 9 deaths from leukemia with 2.7 expected, an SMR of 337

Advantages: fast, inexpensive 1-2 years
exposure based
profile of effects (all causes of death)
relatively free of bias (systematic error)

Limitations: inadequate exposure-possible (info terrible)
inadequate exposure documentation - usual
prone to chance -
prone to confounding alternative cause

B. The case-control design not often used for RA considered not very precise

Example: 138 adults with leukemia, resident in Olmsted County MN, were compared with 276 adults without leukemia. Information on benzene exposure was abstracted from medical records. Among persons with benzene exposure, the RI of leukemia was 3.3 compared to persons without exposure.

Advantages: fast 6 months
profile of exposures
control confounding
precise (not prone to chance)
suitable for rare disease

Limitations: single disease
only relative measures of disease
prone to bias - difficult to prove the controls are truely the same as the cases

VII. Interpretations - How do these influence outcome

A. Chance - make study large

B. Bias - try to deal with possible biases in design phase

C. Confounding - gather lots of data on other known diseases

D. Valid
causal
null

Comment: not mutually exclusive
not permanent

VIII. Causality

A. Individual study
strength
internal consistency
biological credibility

B. Abstract, general case
external consistency
response to manipulation

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C. Specific individual case - for torte cases
relevant exposure
absence of alternative cause

IX. Benzene and leukemia - A model risk assessment

A. Basic science
not genotoxic - not a mutagenic
damages chromosomes - not clear by what mechanism

B. Animal studies
carcinogenic
leukemogenicity problematic

C. Epidemiologic studies 17 studies → 14 pos, 2 neg, 1 ?
generally positive for AML negative for other leukemia
poor quantification of exposure
some potential confounding - other solvents
all studies = weak est on exposure

D. Epidemiologic data*
- observed deaths: leukemia 19
- expected deaths: 9.6
- total deaths: 1273
- mean cum. exposure: 42 ppm-yrs
intensity level × years

E. Risk assessment
- excess deaths: 19-9.6 = 9.4
- excess deaths/1000: 9.4/1.273 = 7.4/1000 - exposed
- baseline risk: 7/1000
- doubling dose:
(14/14.7)(42 ppm-yrs) = 40 ppm-yrs
how much does he need to be exposed to double the risk
20ppm for 2 yrs

X. The OSHA standard

A. For many years
= 10 ppm 8 hr TWA
30 yrs x 10 ppm = 300 ppm-yrs
≃ 7 doublings = 800/1000 = unacceptable
≃7 additions ≃ 56 deaths/1000

B. Currently = 1 ppm 8 hr TWA
30 ppm yrs
≃ 1.75 baseline ≃ 5 excess deaths/1000 exposed

30

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C. Issues – Model Assumes –
- linear dose response
- non-threshold
- other

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Philip Cole, M.D.

Austin H, Delzell E, Cole P: Benzene and leukemia: A review of the literature and a risk assessment. Am J Epidemiol 127:419-439, 1988.